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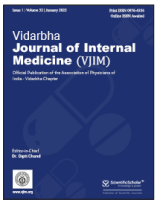

Review Article

Osteoporosis

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ABSTRACT

Bone is a dynamic tissue that is remodelled constantly throughout life. The arrangement of compact and cancellous bone provides strength and density suitable for both mobility and protection. Osteoporosis is defined as a reduction in the strength of bone that leads to an increased risk of fractures. The World Health Organisation operationally defined osteoporosis as a bone density also referred to as a T-score of <−2.5 and is associated with increased risk of fractures. Bone remodelling is regulated by multiple hormones, including oestrogens (in both genders), androgens, Vitamin D and parathyroid hormone (PTH), as well as locally produced growth factors, such as IGF-I, transforming growth factor β, PTH-related peptide (PTHrP), interleukins, prostaglandins and members of the tumour necrosis factor superfamily. The risk of fracture can be predicted by the Fracture Risk Assessment score. Several non-invasive techniques are available for estimating skeletal mass or bone mineral density including single energy X-ray absorptiometry, dual-energy X-ray absorptiometry, quantitative computed tomography and ultra-sound. Total daily calcium intakes <400 mg are detrimental to the skeleton. The recommended daily required intake of 1000–1200 mg for adults accommodates population heterogeneity in controlling calcium balance. For optimal skeletal health, serum 25(OH)D should be >75 nmol/L (30 ng/mL). Bisphosphonates have become the mainstay of osteoporosis treatment. Calcitonin preparations are approved by the FDA for osteoporosis in women >5 years past menopause. Denosumab was approved by the FDA in 2010. Parathormone analogues augment trabecular bone mineral density and reduce fracture occurrence. PTH (1–34) (teriparatide) produced substantial increments in bone mass. Abaloparatide is a synthetic analogue of human PTHrP, which has significant homology to PTH and also binds the PTH Type 1 receptor increasing the bone mass. Ageing is associated with progressive decline in overall muscle strength and bone loss. Resistance training increases bone strength and density, reducing the risk of fracture during a fall. Increased levels of endurance, strength and balance with exercises increase the threshold for disability and dependence as we age. Inactive and sedentary lifestyle should be discouraged. Treatment accessibility could be improved and treatment adherence should be encouraged.

Keywords: Osteoporosis, Silent killer, Bisphosphonates, Teriparatide

INTRODUCTION

Bone is a dynamic tissue that is remodelled constantly throughout life. The arrangement of compact and cancellous bone provides strength and density suitable for both mobility and protection. Compact or cortical bone forms the roughly cylindrical shell of long bones; cancellous or trabecular bone forms the plate-like meshwork that internally supports the cortical shell. Remodelling of bone is accomplished by two distinct cell types: Osteoblasts produce bone matrix, regulate its mineralisation and osteoclasts resorb the matrix. Osteocytes are the terminal differentiated cells derived from osteoblasts after incorporation into newly formed bone tissue. In adults, the more mature bone is organised with fibre bundles regularly arranged in parallel or concentric sheets (lamellar bone). Remodelling of bone continues throughout life and 18% of the total skeletal calcium is deposited and removed each year [Figure 1].

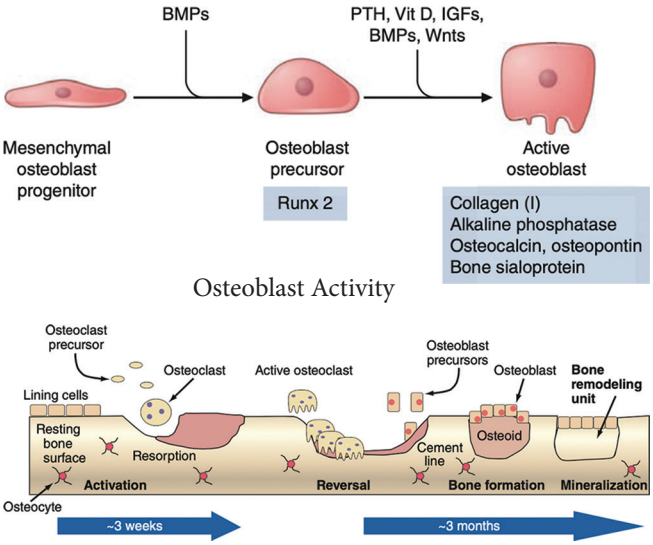

Figure 1: Osteoclast Activity

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Received: 06 July 2022 **Accepted:** 16 July 2022 **Published:** 10 August 2022 **DOI**: 10.25259/VJIM_23_2022

Osteoporosis represents a relevant global public health problem, which is projected to increase in magnitude in the next 10 years mainly in relation to the raging population. It is defined as a reduction in the strength of bone that leads to an increased risk of fractures. Loss of bone tissue causes deterioration in skeletal microarchitecture, and thus, the process of bone loss causes a greater detriment to bone strength than might be appreciated from the simple measure of bone 'density.' The World Health Organisation (WHO) operationally defined osteoporosis as a bone density that falls 2.5 standard deviations or more below the mean for young healthy adults of the same sex and race also referred to as a T-score of core World Health Organisation (WHO) operationally defined osteoporosis as a bone density that falls 2.5 standard deviations or more below the mean for young healthy adults of the same sex and race also referred to as defined as fractures of any bone in adults that occur in the setting of trauma less than or equal to a fall from standing height, with the exceptions of fingers, toes, face and skull.

Osteoporosis is associated with increased risk of fractures, especially those of the hip and vertebrae, that exponentially increases with advancing age. Hip fractures need hospital admission and emergency surgical intervention. This is associated with a high incidence of mortality and morbidity, with 20–25% of patients dying in the year following the injury. Vertebral fractures are a major sign of skeletal fragility, they rarely require hospitalisation, but are associated with risk of further fractures. Vertebral fractures lead to height loss (often of several inches), kyphosis, secondary pain and discomfort related to altered biomechanics of the back. Thoracic fractures can be associated with restrictive lung disease, whereas lumbar fractures are associated with abdominal symptoms that include distention, early satiety and constipation. Cigarette smoking, oestrogen deficiency (early menopause), poor nutrition with low calcium and Vitamin D intake, alcoholism, inadequate physical exercise, rheumatoid arthritis and frailty increase the risk of osteoporosis.[1,2]

Bone remodelling helps to: (1) Repair microdamage within the skeleton to maintain skeletal strength and ensure the relative youth of the skeleton and (2) to supply calcium when needed from the skeleton to maintain serum calcium. There is a well-coordinated activity of osteoblasts, osteoclasts and osteocytes. Osteoblasts are derived from mesenchymal cell lineage and osteoclasts from monocyte/macrophage lineage. Remodelling sites are discrete units, with osteoclasts initiating the process by removal of bone tissue and osteoblasts synthesising new organic bone that becomes gradually mineralised.

Bone remodelling is regulated by multiple hormones, including oestrogens (in both genders), androgens, Vitamin D and parathyroid hormone (PTH), as well as locally produced growth factors, such as IGF-I, transforming growth factor β, PTH-related peptide (PTHrP), interleukins, prostaglandins and members of the tumour necrosis factor superfamily. These factors primarily modulate the rate at which new remodelling sites are activated, a process that results initially in bone resorption by osteoclasts, followed by a period of repair during which new bone tissue is synthesised by osteoblasts. The cytokine responsible for communication between the osteoblasts, other marrow cells and osteoclasts is receptor activator of nuclear factor-κa (RANK) ligand (RANKL). After the age of 30uclear factor-teoblasts, other marrow cellsare activated, a process and resorption exceeds formation resulting in permanent loss of tissue and disrupted skeletal architecture leading to increased risk of osteoporosis-related fractures.[1,2]

Total daily calcium intakes <400 mg are detrimental to the skeleton. The recommended daily required intakes of 1000– total daily calcium intakes <400 population heterogeneity in controlling calcium balance. High intakes primarily from supplement sources appear to result in a greater risk of renal stones and perhaps cardiovascular calcifications (although the literature is inconsistent and controversial). Increasing calcium intake above this level does not improve calcium homeostasis or bone formation. Increasing calcium intake by itself will not prevent bone loss due to other factors (e.g., postmenopausal status).

For optimal skeletal health, serum 25(OH)D should be >75 nmol/L (30 ng/mL). This requires skin exposure to sunlight (estimated to be exposure of face and arms for at least 1 1/2 h each day) or an intake of at least 800–e each day or even higher in individuals with risk factors (as above). Vitamin D insufficiency leads to compensatory secondary hyperparathyroidism and is an important risk factor for osteoporosis and fractures.

Oestrogen also plays a role in determining the life span of bone cells by controlling the rate of apoptosis. Oestrogen deficiency particularly affects the trabecular bone; hence, vertebral fractures are early skeletal consequences.

Inactivity, such as prolonged bed rest or paralysis, results in significant bone loss. Concordantly, athletes have higher bone mass than non-athletes. When exercise is initiated during adult life, the effects of moderate exercise on the skeleton are modest. It is argued that more active individuals are less likely to fall and are more capable of protecting themselves upon falling, thereby reducing fracture risk. Continuing physical activity into the later years appears to slow cognitive decline, another major reason for including exercise programs for the ageing population.

Both Type 1 and Type 2 diabetes mellitus are associated with an increased fracture risk, with increased risk at higher bone density than in the non-diabetic population. This may be due

to differences in the chemical composition of bone tissue that is more brittle than normal, a predilection for conversion of precursors to adipose cells rather than osteoblasts and the sequelae of diabetes that increase the risk of falls and injury. Severe bone loss occurs in quadriplegic and paraplegic individuals below the level of the injury. The combination of loss of muscle function and innervation of both muscle and bone contributes to failure to recover mobility, which leads to a high fracture risk in those attempting to pursue athletic activities despite their primary diagnosis (e.g., wheel-chair athletes). Bone loss also follows a stroke and is again dependent on the severity of the paralysis.[2-4]

A large number of medications used in clinical practice have potentially detrimental effects on the skeleton including corticosteroids, anticonvulsants, cyclosporin, tacrolimus, excessive doses of thyroid supplementation, aromatase inhibitors, SSRIs, heparin, lithium, proton pump inhibitors and thiazolidinediones result in rapid loss of bone and increased fracture risk. Other potential factors being smoking, excessive alcohol intake and COPD. Myeloma can masquerade as generalised osteoporosis, although it more commonly presents with bone pain and characteristic 'punched-out' lesions on radiography. Serum and urine electrophoresis and/or evaluation for serum free light chains in urine are required to exclude this diagnosis.

EVALUATION

The risk of fracture can be predicted by the Fracture Risk Assessment (FRAX) score. It integrates clinical risk factors and bone mineral density at the femoral neck to calculate the 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture). The parameters included in a FRAX assessment are: Country, age, sex, weight, height, previous fracture, hip fracture in the subject's mother or father, smoking, glucocorticoid treatment, rheumatoid arthritis, disease strongly associated with osteoporosis, alcohol intake of three or more standard drinks per day and bone mineral density (BMD) of the femoral neck.[5]

Several non-invasive techniques are available for estimating skeletal mass or bone mineral density including single energy X-ray absorptiometry, dual-energy X-ray absorptiometry, quantitative computed tomography (CT) and ultra-sound.

DXA is a highly accurate X-ray technique that has become the standard for measuring bone density. It is the standard practice to relate the results to 'normal' values using T-scores (a T-score of 1 equals 1 SD), which compare individual results to those in a young adult population that is matched for race and sex. The mean value is given a score of zero and the range +2.5 to –2.5 (i.e., 2.5 SDs above or below the mean). Z-scores (also SDs) compare individual results to those of an age- and gender-matched reference population. Thus, a 60-year-old woman with a Z-score of –1 (1 SD below mean for age) has a T-score of –2.5 (2.5 SD below mean for a young control group). A T-score <–2.5 in the lumbar spine, femoral neck or total hip has been defined as osteoporosis. DXA measures mass (an estimate of the mineral in bone) is not architecture. Recent addition of the trabecular bone score (TBS) in DXA measurements is an attempt to capture these architectural changes. The TBS is calculated using an analytical tool that processes the grey level texture of normal DXA scans to estimate trabecular microarchitecture.

Hip-axis length (HAL), hip-strength analysis (HSA) and finite element analysis (FEA) are other methodologies that, similarly to TBS, can be obtained from DXA analysis. The longer the HAL the higher the risk of fracture is, independently from other clinical and densitometric risk factors. The HSA derives from the analysis of the femoral neck cross-sectional area and cross-sectional moments of inertia. The HSA estimates the cortical stability in buckling and represents an index of structural rigidity. FEA estimates the microarchitectural geometry of the hip and can be used to study the behaviour of bone in relation to mechanical loading.

Radiofrequency echographic multispectrometry is an innovative approach that uses ultrasound to analyse BMD. Thirty-six raw and unfiltered ultrasound images of lumbar spine and femoral neck are analysed by a software to provide a DXA-equivalent BMD value.

High-resolution peripheral quantitative computed tomography (HRpQCT) is an alternative imaging technique that can provide both quantitative and qualitative information regarding the skeleton. However, HRpQCT is an expensive technology and as such its use might be limited in clinical practice.

The osteoblast activity can be assessed by measuring the biochemical markers for bone formation such as – Serum bone-specific alkaline phosphatase, serum osteocalcin and serum propeptide of Type I procollagen.

Osteoclast activity can be assessed by measurement of products of collagen degradation and bone resorption such as urine and serum cross-linked N-telopeptide and C-telopeptide.

TREATMENT

Treatment of a patient with osteoporosis frequently involves management of acute fractures as well as treatment of the underlying disease. Hip fractures almost always require surgical repair if the patient is to become ambulatory again. Vertebral fractures may be managed conservatively with NSAIDs, Calcitonin or a technique that involves percutaneous injection of artificial cement (polymethylmethacrylate) into the vertebral body (vertebroplasty or kyphoplasty). Narcotic

analgesics, physical modalities, such as ultrasound and transcutaneous nerve stimulation, may be beneficial in some patients.

Management of underlying disease is important with risk factor reduction and optimal calcium supplementation, with adequate total calcium intake (1000 mg/day for men aged 50–optimal calcium supplementation, 51 years and men s71 years). Vitamin D targeting a serum levels of >30 ng/ml. The 24-h urinary calcium excretion should be in the range of 10,000,000 mg/day. The lower levels suggest problems with adherence to the treatment regimen or with absorption of calcium or Vitamin D supplements. Urinary calcium levels >250 mg/24 h predispose to nephrolithiasis and should lead to a reduction in Vitamin D dosage and/or calcium supplementation.

Vitamin K is required for optimal carboxylation of osteocalcin. Magnesium supplementation is warranted in patient with inflammatory bowel disease, celiac disease, malnutrition and alcoholism. Weight-bearing exercise helps prevent bone loss but does not appear to result in substantial gain of bone mass; however, exercise has beneficial effects on neuromuscular function and it improves coordination, balance and strength, thereby reducing the risk of falling.

Epidemiologic databases indicate that women who take oestrogen replacement have a 50% reduction, on average, of osteoporosis-related fractures, including hip fractures. Tamoxifen and Raloxifene reduce bone turnover and bone loss in postmenopausal women compared with placebo.

Bisphosphonates have become the mainstay of osteoporosis treatment. Alendronate, risedronate and zoledronic acid are approved for the prevention and treatment of postmenopausal osteoporosis, steroid-induced osteoporosis and osteoporosis in men. Two side effects with bisphosphonates have been described – the first is osteonecrosis of the jaw (ONJ). ONJ usually follows a dental procedure in which bone is exposed (dental extractions and implants), where it is presumed to be infected and dies. Second is an atypical femur fracture in the subtrochanteric femoral region or across the femoral shaft distal to the lesser trochanter after a trivial trauma. Bisphosphonates are structurally related to pyrophosphates, compounds that are incorporated into bone matrix. Bisphosphonates specifically impair osteoclast function and reduce osteoclast number, in part by inducing apoptosis.

Calcitonin preparations are approved by the FDA for osteoporosis in women >5 years past menopause. It suppresses osteoclast activity by direct action on the osteoclast calcitonin receptor.

Denosumab was approved by the FDA in 2010 for the treatment of postmenopausal women who have a high risk for osteoporotic fractures, including those with a history of fracture or multiple risk factors. Denosumab is a fully human monoclonal anti-body to RANKL, the final common effector of osteoclast formation, activity and survival.[1,6]

Parathormone analogs augment trabecular BMD, it increases bone mass and reduce fracture occurrence. PTH (1–34) (teriparatide), when superimposed on on-going oestrogen therapy, produced substantial increments in bone mass (13% over a 3-year period compared with oestrogen alone). Teriparatide produces rapid and robust increases in bone formation and then bone remodelling overall, resulting in substantial increases in bone mass and improvements in microarchitecture, including cancellous connectivity and cortical width. In women with painful acute osteoporotic vertebral fractures, teriparatide reduced subsequent vertebral fractures by ~50% compared with risedronate. Teriparatide heals the fracture and may preclude the need or surgical repair. It has direct actions on osteoblast activity, with biochemical and histomorphometric evidence of *de novo* bone formation within a week or two in response to teriparatide.[7]

Abaloparatide is a synthetic analogue of human PTHrP, which has significant homology to PTH and also binds the PTH Type 1 receptor. Abaloparatide and teriparatide exert different binding affinities to the two different receptor conformations, R^0 and RG. Compared to teriparatide, abaloparatide binds with similar high affinity to the RG conformation but with much lesser affinity to the R^0 conformation. These differences appear to result in a similar bone formation stimulus but lesser bone resorption stimulus. Teriparatide is also approved for the treatment of glucocorticoid-induced osteoporosis.[1,7]

Pharmacological treatments are the mainstream of fracture prevention. Local osteo-enhancement procedure (LOEP) is an emerging surgical procedure that has been shown to effectively reduce the risk of refracture. LOEP involves the implantation of an osteoconductive, calcium-based and material in the skeleton. The implant is rapidly incorporated and gives biomechanical benefit.[6]

CONCLUSION

Ageing is associated with progressive decline in overall muscle strength and bone loss. Bone deterioration happens silently and progressively and is labelled by the WHO as one of the silent killers. Precise fracture risk assessment tools will change our ability to detect patients at high risk of fractures. Effective interventions are needed to help mitigate the challenges posed by increased osteoporosis prevalence. Resistance training increases bone strength and density, reducing the risk of a fracture during a fall. Increased levels of endurance, strength and balance with exercises, increase the threshold for disability and dependence as we age. Inactive and sedentary lifestyle should be discouraged. Regular exercise for at least 30 min each day also improves one's overall mood and mental health. Treatment accessibility

could be improved and treatment adherence should be encouraged.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Mitra S, Mitra R. Osteoporosis. Vidarbha J Intern Med 2022;32:115-9.